# Neurobiological and Clinical Consequences of Stress

## From Normal Adaptation to Post-Traumatic Stress Disorder

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# Hypothalamic-Pituitary-Adrenal Functioning in Post-Traumatic Stress Disorder

## Expanding the Concept of the Stress Response Spectrum

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This chapter will review the literature on hypothalamic-pituitary-adrenal (HPA) axis functioning in post-traumatic stress disorder (PTSD). The conclusion that will emerge from a review of these findings is that the alterations that have been noted in PTSD differ dramatically from those that have been described in most studies of the normative stress response. Furthermore, the HPA axis findings in PTSD are distinct from those reported in other psychiatric conditions, even conditions with similar symptoms to PTSD, such as major depressive disorder. A model of HPA axis functioning that has been put forth to explain these alterations will be described.

The distinctness of the HPA axis findings in PTSD raises two basic conceptual issues that will also be the focus of discussion. The first issue bears on the formulation of PTSD as a normative consequence of stress. Clearly, the unusual nature of the alterations observed in this stress-responsive system challenges us to reexamine the clinical phenomenology of PTSD in order to evaluate the extent to which this disorder may also represent an atypical reaction to extreme stress. The second issue raised concerns the narrowness of current formulations of the normative stress response. The HPA axis findings in PTSD challenge us to widen our perspective on the stress response spectrum.

## CURRENT CONCEPTUALIZATIONS OF PTSD AND THEIR INFLUENCE ON BIOLOGICAL HYPOTHESES

The inclusion of PTSD as a psychiatric disorder in the DSM-III (1) represented a rediscovery in how the field of psychiatry viewed the mental health consequences following exposure to trauma. In essence, the diagnosis of PTSD acknowledged that exposure to trauma precipitated serious and long-lasting symptoms in normal individuals. Prior to this formulation, there was no clear distinction between exposure to a stressor versus exposure to a traumatic event. Thus, the focus was on describing a set of mental health

consequences that could occur independently of the nature and severity of the stressor. Regardless, the presence of longlasting psychiatric symptoms following either type of event was seen as developing only in vulnerable individuals, perhaps as secondary to preexisting personality traits or other constitutional risk factors. On the other hand, descriptions such as "gross stress reaction" in the DSM-I (2) and terms such as "war neurosis" (3) acknowledged that psychiatric symptoms could develop in response to trauma. However, these responses were seen as anomalous maladaptations.

The DSM-II contained descriptions of "transient situational disturbance" (4), which was the diagnostic forerunner of what are now called "adjustment disorders." The underlying assumption of these disorders was that normative reactions to stress would be characterized by quick recovery. On the other hand, prolonged responses to trauma were viewed as anxiety or depressive neuroses, and were conceptualized as having roots that predated the occurrence of the trauma (4). Thus, PTSD as described in DSM-III, and more recently in DSM-IV (5), represented an important departure from the "stress disorders" described in prior diagnostic schemata in viewing chronic and debilitating illness following trauma as a consequence of the nature of the traumatic event, even in individuals without constitutional vulnerability.

Importantly, because the symptoms of PTSD were essentially conceptualized as describing a normative response to extreme stress, many biological studies of PTSD—certainly earlier investigations—had as their major impetus and rationale the hypothesis that alterations observed in symptomatic individuals would be analogous to those observed in animal and human studies of stress (6–9).

## THE PARADIGM OF THE BIOLOGICAL STRESS RESPONSE

Selye's initial characterization of the biological stress response in 1936 formed the basis of an influential paradigm in the field of science that continues to pervade modern conceptualizations of the changes that occur during and after exposure to a stressor (10). The original observations, which have withstood the test of time, were that provocation by a wide range of "stressors" would result in a complex psychoneuroendocrine response, part of which was an increased release of pituitary-adrenocortical hormones. Selye also described the fact that stress left indelible marks on the organism, and that cumulative stress effects would have a substantial impact on the reservoir of "adaptational energy" that influenced biological adaptation (11).

An important component of the Selye model of stress was that any potential stressor could invoke the stress response. In fact, the presence and magnitude of a stressor could be inferred by the presence and magnitude of the pituitary-adrenocortical response. Therefore, Selye's focus was not on the objective nature of any particular stressor per se but rather on the universality of the stress response. In this context it is interesting that Selye's formulation was quite different from the original focus of the DSM-III on the nature of the traumatic event (i.e., as needing to fulfill the magnitude and severity implicit in "Criterion A"). The inclusion of a caveat to Criterion A in the DSM-IV regarding the fact that a stressor must have elicited a behavioral response of fear and helplessness is more compatible with Selye's notion of the importance of subjective responses to stress.

Selye's observations sparked more than half century of research that aimed to further elucidate the basic neurophysiology of the stress response. What emerged from decades of research has been information regarding: 1) neuromodulators that stimulate and attenuate the release of stress hormones; 2) how the release of HPA axis hormones modifies other biochemical reactions in response to stress; 3) how characteristics of stressors, such as their intensity and frequency, influence the stress response; 4) factors that can influence resilience or vulnerability to stressors; and 5) medical and psychiatric consequences of alterations in normal HPA axis activity. More recently, knowledge has accrued regarding the myriad cellular and molecular changes induced

by stress. Many of these topics are reviewed in other chapters in this volume.

Despite the addition of this knowledge, the basic stress response is still defined by the strength of pituitary-adrenocortical activity. It has now become clear, however, that a complex interplay of neuromodulators influences this response. For example, stress-activated neurotransmitter systems in the brain release corticotropin-releasing factor (CRF) from the hypothalamus and other areas of the brain, presumably in a dose-dependent fashion (see review [12]). Release of adrenocorticotropin hormone (ACTH) from the portal system of the anterior pituitary and cortisol from the adrenals is stimulated by CRF and cosecretagogues such as arginine vasopressin (see review [13]). Cortisol and other glucocorticoids then initiate the suppression of other immune, metabolic, and neural defensive reactions that occur in response to stress, and also act via a negative feedback loop to the hippocampus, hypothalamus, and pituitary to regulate subsequent hormone release (12). A variety of neuromodulators and neuropeptides additionally exert negative feedback and regulatory effects on the target organs of the HPA axis (see review [13]). The immune, metabolic, and neural defensive biological responses that occur in response to stress are important for the short-term response to stress, but produce long-term damage to the organism if they are not eventually terminated (14). For example, prolonged, elevated concentrations of glucocorticoids can be toxic, and are associated with several other detrimental consequences such as neuronal death (15), medical diseases (16), and impaired affect and cognitive alterations (17).

It has also become clear in recent years that several factors such as the objective nature of the stressor, the individual's prior stress history, and genetic and environmental modifiers can determine or modify the pituitary-adrenocortical response to stress (18,19). These findings have challenged the unidirectional, dose-dependent increases in pituitary-adrenocortical hormones that currently define the basic stress response (20). In this chapter, we summarize the literature on the HPA axis in PTSD, and consider the

extent to which current models of stress responsivity can be informative in understanding the particular type of stress response present in individuals with this diagnosis.

## HPA AXIS ALTERATIONS IN PTSD

Consistent with initial hypotheses, most studies to date have demonstrated significant differences in HPA axis parameters in PTSD sufferers compared to normal controls. However, the direction in which the system has been found to be altered is contrary to early predictions; the findings have demonstrated substantial differences in HPA axis parameters in PTSD compared to those described in preclinical and clinical studies of stress, and psychiatric disorders such as major depression. Many of the results are summarized in Tables 1 and 2.

### Studies of Urinary Cortisol

Four of five studies performed to date have demonstrated that individuals with PTSD show evidence of low cortisol levels. The first series of investigations described differences in mean 24-hour urinary cortisol excretion between patients with PTSD compared to patients with

**TABLE 1.** *A summary of findings of HPA axis alterations in PTSD compared to normal comparison group*

| Baseline measures | |
| --- | --- |
| 24-hr urinary cortisol excretion | ↓ |
| Plasma cortisol levels | ↓ |
| Cortisol regulation ("signal-to-noise" ratio) | ↑ |
| Lymphocyte glucocorticoid receptor number | ↑ |

| Response to neuroendocrine challenge | |
| --- | --- |
| Dexamethasone | |
|   1.00 mg | same |
|   0.50 mg | ↑ |
|   0.25 mg | ↑ |
| Response to CRF | ↓ |
| Response to metyrapone stimulation | ↑ |

CRF, corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenal; PTSD, post-traumatic stress disorder.

**TABLE 2.** *A summary of findings of HPA axis alterations in PTSD compared to trauma-exposed comparison group*

| Baseline measures | |
|---|---|
| 24-hr urinary cortisol excretion | ↓, ↑ |
| Lymphocyte glucocorticoid receptor number | ↑ |

| Response to dexamethasone challenge | |
|---|---|
| 0.50 mg | ↑ |
| 0.25 mg | ↑ |

HPA, hypothalamic-pituitary-adrenal; PTSD, post-traumatic stress disorder.

other psychiatric diagnoses and to normal controls. In an initial investigation, lower mean 24-hour urinary cortisol excretion was observed in nine inpatient combat veterans with PTSD compared to patients with major depressive disorder, bipolar mania, paranoid schizophrenia, and undifferentiated schizophrenia (21). These findings were replicated and extended in two other studies examining urinary cortisol excretion in a similar population (i.e., treatment-seeking Vietnam war veterans with PTSD). In one study, urinary cortisol excretion was found to be significantly lower in combat-veteran inpatients with PTSD compared to inpatients with major depression, bipolar mania, schizophrenia, and panic disorder (22). Another study comparing urinary cortisol excretion in treatment-seeking combat veterans with PTSD to nonpsychiatric healthy controls found urinary cortisol excretion to be lower in the PTSD group (23). Importantly, this study also showed no differences in urinary cortisol excretion between outpatients and inpatients, or between PTSD with and without MDD.

In contrast to the findings just cited, another group found that urinary cortisol excretion was significantly higher in combat veterans with PTSD compared to combat veterans without PTSD (6). The mean cortisol excretion reported was 107 μg/day for the PTSD group and 80.5 μg/day for the combat controls. These values are at the very high end of the normal 24-hour cortisol excretion (i.e., normal range of cortisol is considered to be 20–90 μg/day) and between two- and threefold higher than those reported for both PTSD and normals in the two other published studies (i.e., in Mason et al.'s study,

the mean urinary cortisol was 33 μg/day, and in the Yehuda et al. studies the means were 42 μg/day and 39 μg/day for the PTSD group). The relatively high cortisol values in this study may have been due to the fact that urine specimens were collected in acid preservative (which may promote hydrolysis of the unconjugated cortisol and/or interfere with the antibody-antigen reaction in the radioimmunoassay procedure, thus yielding artificially high cortisol values (24)). Another important difference between this and the aforementioned studies of urinary cortisol excretion was in the use of a trauma-exposed, non-PTSD comparison group. The inclusion of a trauma-exposed non-PTSD group is essential to biological studies because it allows a differentiation between hormonal differences relating to exposure to trauma and hormonal differences specifically related to PTSD. Given the increasing recognition that most individuals who experience trauma do not develop PTSD, it is reasonable to expect differences in stress-responsive biological differences between these two groups. In the Pitman and Orr study (6), the direction of cortisol secretion in the PTSD group was different when a trauma-comparison group was used instead of a psychiatric or normal control group. Unfortunately, because the authors did not include a nontrauma-exposed control group, it was not possible to determine the extent to which the combat-exposed groups differed from nonexposed subjects.

More recently, 24-hour urinary cortisol excretion was measured in a group of nontreatment-seeking Holocaust survivors with PTSD, a group of Holocaust survivors without PTSD, and a demographically-matched nonpsychiatric control group (25). Because both trauma-exposed individuals without PTSD and nonexposed individuals were studied and compared to normals, it was possible to evaluate the extent to which cortisol levels were related to trauma exposure versus the presence of PTSD symptoms. The results demonstrated that Holocaust survivors with PTSD had a significantly lower mean urinary cortisol excretion as compared with the other two groups. The survivor groups without PTSD showed levels that were statistically similar to those of nonexposed controls.

To determine whether cortisol levels in PTSD represented "trait-related" or "state-related" variables, additional analyses were performed. In the first analysis, the Holocaust survivor group without PTSD was further subdivided into those meeting and those not meeting the criteria for past PTSD. There was no significant difference in mean 24-hour cortisol excretion between these two groups. A second set of analyses using multiple correlation revealed a significant relationship between cortisol excretion and severity of PTSD, as determined by the Clinicians Administered PTSD Scale, that was due to a substantial association with scores on the avoidance subscale. It was concluded that low urinary cortisol levels do not appear to be a function of exposure to trauma per se but rather are related to the current severity of PTSD.

The study of Holocaust survivors also provided information about several other aspects of urinary cortisol excretion in PTSD that had not been determined in previous studies of Vietnam veterans.

1. Because both men and women were studied, potential gender differences in cortisol levels in women with PTSD were examined. Results revealed no significant gender effects on cortisol in any of the groups studied.
2. It was possible to address the issue of the persistence of the low cortisol levels in PTSD. Holocaust survivors with PTSD were studied 50 years after their exposure to the Holocaust, compared to Vietnam veterans who were studied 20 to 25 years following exposure to combat. Because low cortisol levels were present in individuals who sustained a focal trauma over 50 years prior to the biological assessment, it was concluded that low cortisol levels may persist for decades in symptomatic individuals.
3. Substance abuse and the presence of other psychiatric diagnoses could have possibly contributed to the biological alterations in combat veterans with PTSD. The study of community-dwelling Holocaust survivors provided the opportunity to explore whether cortisol levels would be low in a sample of individuals with PTSD who were not treat-

ment seekers, who did not have other psychiatric conditions requiring inpatient or outpatient mental health interventions, who had no past or current substance abuse behavior at all, and who showed good vocational, occupational, and social functioning. The fact that urinary cortisol excretion was lower in this type of sample with PTSD mitigates the numerous criticisms that have often been applied to biological studies of combat veterans (e.g., that biological alterations observed may be artifacts of psychiatric, occupational, and social problems). The presence of these potentially confounding variables in combat veterans do not seem to be related to the low cortisol levels in PTSD.

Studies of nonveteran trauma survivors are particularly critical to a fuller understanding of the HPA axis in PTSD because they allow a consideration of whether biological changes reflect differences in the type of traumatic experiences sustained or the characteristics of the sample being studied. Indeed, in the stress literature numerous studies have showed differences in biological parameters as a function of the specific nature of the stress paradigm. To the extent that biological alterations are related to the presence of a stress disorder and not exposure, differences in HPA axis parameters should not be present as a function of the type of traumatic event that has given rise to the disorder. Therefore, it will be important in future studies to systematically explore potential abnormalities in cortisol secretion as a function of type of trauma sustained.

## Studies of Plasma Cortisol and ACTH

Determinations of plasma cortisol and ACTH levels using a single sample obtained by routine venipuncture are not considered to accurately reflect hormone concentration, because the stress of the blood withdrawal procedure itself can cause fluctuations in hormone levels. Not surprisingly, studies using this method of assessment have observed increases (26), decreases (27), or no differences (28–29) in cortisol

levels in PTSD subjects compared to control groups.

Two studies reported ACTH levels in PTSD patients that were comparable to those of a normal comparison group (8,26). However, in addition to the caveat in the previous paragraph regarding the use of a single venipuncture sample, it is difficult to accurately assess the pituitary activity based on blood concentrations of ACTH due to negative feedback influences on the pituitary. Because the pituitary gland mediates between hypothalamic stimulation of the pituitary by CRF and inhibition of ACTH resulting from the negative feedback of adrenal corticosteroids, baseline ACTH levels may indeed appear to be "normal," even though the pituitary gland is receiving excessive stimulation from CRF (30). Therefore, plasma ACTH levels do not really provide much information about the regulation or activity of the HPA axis, especially if they appear to be "normal" in the face of other alterations.

More recently, the circadian release of cortisol over the 24-hour diurnal cycle was examined in outpatients with combat-related PTSD, normal controls, and outpatients with major depression. In this study, following an overnight stay in the clinical research center, an i.v. was inserted and blood samples were withdrawn every 30 minutes for a 24-hour period while the subject remained at bed rest and in a fasted state (until 6:00 PM). Under these conditions, basal plasma cortisol release was found to be significantly lower, primarily in the late evening and very early morning hours in the PTSD group (31). Chronobiological analysis of the raw cortisol levels using multioscillator cosinor modeling revealed a greater degree of circadian rhythm and a higher signal-to-noise ratio of cortisol release in subjects with PTSD. That is, relative to lower cortisol excretion, PTSD patients tended to show cortisol fluctuations that were high. These data were interpreted as reflecting a more dynamic HPA axis in PTSD in that this neuroendocrine system may now be more sensitive to environmental stimuli. Future studies exploring the circadian release of other neuropeptides would increase our understanding of this axis and its regulatory influences.

## Lymphocyte Glucocorticoid Receptors

Steroid-receptor-binding parameters are important in interpreting studies examining basal hormone secretion, because hormones cannot exert their genomic effects unless they are bound to steroid receptors (32,33). Because lymphocytes and brain glucocorticoid receptors share similar regulatory and binding characteristics, it has been suggested that lymphocyte glucocorticoid receptor function reflects aspects of both peripheral and central cortisol regulation (34, 35).

Results from three studies have now demonstrated a significantly larger number of lymphocyte glucocorticoid receptors in combat veterans with PTSD compared to nonpsychiatric and psychiatric comparison groups with major depression, panic disorder, bipolar mania, and schizophrenia (22,27,36). The finding of a larger number of glucocorticoid receptors is consistent with observations of low cortisol in PTSD, in that low circulating levels of a hormone or neurotransmitter are usually associated with an upregulation or increased number of receptors. However, in the case of PTSD, the direction of causality of this relationship is not known. In more classic models of receptor-ligand interactions, changes in glucocorticoid receptor number are conceptualized as reflecting compensatory responses to the concentration of ligand (37–40). According to these models, increased number of glucocorticoid receptors is a secondary consequence of low cortisol. It is alternatively possible, however, that glucocorticoid receptors actually serve to regulate hormonal release by modifying the strength of negative feedback. In this case, the low cortisol levels would be conceptualized as secondary consequences of increased glucocorticoid receptor activity. Knowledge of causality of the relationship between the glucocorticoid receptors and low cortisol is imperative to a deeper understanding of HPA axis alterations in PTSD. If increased glucocorticoid number is conceptualized as a primary alteration in PTSD, this would imply alterations in parameters that are directly related to the activity of glucocorticoid such as negative feedback inhibition. On the other hand, if increased glucocor-

ticoid number in PTSD is secondary to low cortisol levels, then it would be likely that HPA axis alterations in PTSD would be a result of a decreased stimulation of the adrenals and a resultant decrease in the production of cortisol.

The animal stress literature provides only one known model in which glucocorticoid receptors are altered in the direction observed in PTSD. This model is the "early handling" paradigm, in which neonatal animals are exposed to the stress of handling daily for several weeks. Early handling results in a permanent upregulation of hippocampal glucocorticoid receptors (41–44), and a resultant decrease in cortisol following exposure to subsequent stress (45–48). The upregulation of glucocorticoid receptors is rather unusual, because typically glucocorticoid receptors are thought to downregulate following stress (37). The primary alteration in glucocorticoid receptor number is thought to underlie the attenuated cortisol response to stress observed in adult animals who have received neonatal handling (41–44). The observations of altered HPA axis parameters in early handled rats nicely parallels many of the findings observed in PTSD (i.e., not only in regard to the HPA axis but also with respect to alterations in thyroid hormones; early handled animals show increases in T3 and T4 (49) similar to those recently described in PTSD (49a). Thus, the model of early handling provides an interesting basis for further hypothesis testing regarding the true etiology of HPA axis alterations, and in particular glucocorticoid receptor abnormalities, in PTSD. For example, it is currently believed that the early handling manipulation provides a paradigm for how environmental events shape the sensitivity of stress-responsive neuroendocrine systems (50). Implicit in this model is the idea of a developmentally sensitive period in which exposure to environmental events leads to the establishment of a different type of stress response. This notion would be consistent with the observation that combat veterans with PTSD have a higher exposure to stressful events during childhood (51), and raises the possibility that certain features of the HPA axis alterations observed in PTSD (i.e., in particular, alterations in glucocorticoid recep-

tor number) may be present in individuals prior to trauma exposure in adulthood.

It has not been possible to date to examine whether lymphocyte glucocorticoid receptor number is altered in individuals who develop PTSD prior to their exposure to a traumatic event that will induce this disorder. It is also not definitively known whether changes in lymphocyte glucocorticoid receptor number observed in combat veterans with PTSD reflect the fact that these individuals were exposed to stress or, rather, are related to their manifesting a stress disorder. In a preliminary report, it was observed that glucocorticoid receptor number was significantly higher in combat veterans without PTSD compared to normal controls (27). This finding suggests that trauma exposure per se may result in long-lasting changes in glucocorticoid receptors. On the other hand, the number of glucocorticoid receptors in combat veterans who do not meet current diagnostic criteria for PTSD is found to be smaller than that observed in combat veterans with PTSD. Part of the difficulty in reaching an unequivocal conclusion regarding the nature of the alteration in the non-PTSD veteran group is that some of the subjects met the criteria for past PTSD and had some PTSD symptoms. Future studies exploring associations between dose of trauma exposure, PTSD symptoms, and glucocorticoid receptor number are necessary in order to definitively address the cause of glucocorticoid receptor alterations in victims of trauma.

## Neuroendocrine Challenge Studies

Three HPA axis challenge paradigms have been used to study PTSD: the dexamethasone suppression test (DST), the corticotropin releasing factor (CRF) test, and the metyrapone stimulation test.

### Cortisol Response to Dexamethasone:

Studies examining the cortisol response to dexamethasone in psychiatric disorders, most notably major depressive disorder, have repeatedly shown a "nonsuppression" of cortisol (i.e.,

8:00 AM postdexamethasone cortisol levels at or above 5.0 µg/100 dl) in about 40% to 60% of depressed patients (see review [52]). A nonsuppression of cortisol following dexamethasone is thought to result from a reduced ability of glucocorticoids to suppress the release of CRF and ACTH, and/or adrenal cortisol hypersecretion. The cortisol response to 1 mg dexamethasone has been investigated in five studies of PTSD. These studies have all reported that PTSD patients without major depression show a "normal" suppression to dexamethasone (7,9,53–55). However, closer examination reveals that PTSD patients as a group show an exaggerated response to dexamethasone. A recent meta-analysis of the DST literature in PTSD (24) showed that averaging the mean cortisol data across all published studies revealed a cortisol value in nondepressed PTSD subjects of 1.74 µg/dl, a value well below the established cutoff of 5.0 µg/dl.

The findings of cortisol suppression following dexamethasone in PTSD patients with major depression are less clear. In an initial study, Kudler et al. (9) reported that PTSD patients with major depressive disorder showed a rate of nonsuppression comparable with what has been observed in major depressive disorder, whereas Halbreich et al. (7) and Kosten et al. (54) found normal responses to dexamethasone even in depressed combat veterans with PTSD. Olivera and Fero (53) reported a 32% rate of nonsuppression in 65 combat veterans with PTSD who met comorbid criteria for major depressive disorder. However, these individuals showed normal suppression after their major depression had remitted. A study examining the cortisol response to dexamethasone in eight civilian women with PTSD (55) also showed normal responses to dexamethasone. Thus, in averaging the 4:00 PM postdexamethasone cortisol values of the 83 PTSD patients with comorbid depression, the overall mean was somewhat higher than that reported for PTSD patients without major depression, but still well below the cutoff of the 5.0 µg/dl used as a threshold for major depression.

Most of the DST studies in PTSD were conducted before it was appreciated that cortisol levels in PTSD patients tended to be low and the number of glucocorticoid receptors larger than in normals. Therefore, these earlier studies were designed to test for nonsuppression in PTSD, and did not focus on the possibility of a hypersuppression to dexamethasone. However, in the discussion of one of these reports, the possibility of a hypersuppression to following dexamethasone was considered (7). Failure to observe the classic nonsuppression response to cortisol coupled with reported HPA axis alterations that appeared distinct from those in depression led to studies designed to detect a potential enhanced suppression of the cortisol response to dexamethasone.

Recently, the question of enhanced cortisol suppression to dexamethasone was explored using 0.50 mg (27–28) and 0.25 mg (27) dexamethasone. A hyperresponsiveness to low doses of dexamethasone as reflected by significantly lower postdexamethasone cortisol levels was observed in PTSD patients compared to normals. This effect was not due to individual differences in dexamethasone bioavailability. Nor was it due to differences in free versus bound cortisol as determined by measurements of corticosteroid-binding globulin (Yehuda et al., unpublished observations). The enhanced suppression of cortisol was accompanied by a concurrent decline in the number of cytosolic lymphocyte glucocorticoid receptors (27). Interestingly, the hyperresponsiveness to dexamethasone was also present in combat veterans with PTSD who met the diagnostic criteria for major depressive disorder (28) and, importantly, was not present in combat veterans without PTSD (27). Furthermore, the enhanced suppression of cortisol to low doses of dexamethasone has not been described in other psychiatric disorders and has the potential for use as a relatively specific marker for PTSD.

Cortisol suppression to dexamethasone in PTSD patients also appeared to be unrelated to exposure to trauma. Combat veterans without PTSD were indistinguishable from nontraumatized normal males in their responses to both doses of dexamethasone. The failure to observe cortisol hypersuppression in traumatized combat veterans without PTSD indicates that this phe-

nomenon is likely related to the pathophysiology of the disorder and not directly to the severity of the stressor that may have precipitated this condition.

cortisol resulting directly from an increased number of glucocorticoid receptors (GR) on the pituitary gland (60).

## ACTH Response to CRF:

A challenge strategy is necessary to explore the pituitary release of ACTH because, as just described, given the highly regulated nature of the HPA axis, baseline ACTH levels may appear "normal" even in cases where the pituitary gland is being overstimulated by CRF. Use of challenge strategies allows direct assessment of pituitary sensitivity, and then an indirect determination of the regulatory influences that gave rise to this sensitivity. Finally, it is possible from such studies to evaluate the potential consequences of pituitary sensitivity for adrenal release of cortisol.

The CRF challenge test measures the pituitary ACTH and adrenal cortisol response to exogenous infusion of the neuropeptide CRF. In several reports, the ACTH responses to CRF has been reported to be "blunted" in major depression (56–58). It has been suggested that decreased ACTH response to CRF reflects a downregulation of pituitary CRF receptors caused by hypothalamic CRF hypersecretion, or occurs as a result of the increased negative feedback inhibition of the pituitary secondary to high cortisol levels (56–59).

A single study of eight PTSD subjects suggests that the ACTH response to CRF is also blunted (8). Given that several different biological routes can result in ACTH blunting to CRF (59), and considering the already specified differences between PTSD and major depression, it is quite possible that the mechanisms underlying blunted ACTH response in PTSD are different from the mechanism just described for major depression. For example, because the attenuated ACTH response in PTSD patients occurred in the presence of normal, nonelevated evening plasma cortisol levels, it may be that ACTH blunting in response to CRF occurred as a result of a hyperresponsivity of the pituitary gland to

## β-Endorphin and ACTH Response to Metyrapone:

Metyrapone administration represents another way to examine pituitary sensitivity. Metyrapone is a drug that blocks synthesis of cortisol from its immediate precursor, causing a drastic reduction in cortisol levels for several hours. Because of the substantial drop in cortisol levels, negative feedback influences of cortisol on the pituitary are dramatically suppressed. The abrupt disruption of cortisol synthesis results in a sudden and significant increase in release of β-endorphin and ACTH. The normal response to metyrapone results in a two- to fourfold increase in plasma levels of β-endorphin and ACTH within 2 to 8 hours of metyrapone administration. Under these conditions, it is possible to use the concentration of β-endorphin and ACTH as indices of hypothalamic CRF activity (61). If levels of β-endorphin or ACTH are substantially higher (i.e., greater than fourfold increase in response to metyrapone), this is evidence that the pituitary is receiving a greater stimulation by CRF and is now hyperresponsive. If levels of these peptides are substantially lower (i.e., less than twofold increase), this suggests a decreased CRF stimulation of the pituitary, and a resultant pituitary hyporesponsivity.

In a pilot study, metyrapone was administered to 8 combat veterans with PTSD and 10 normal controls. Only 1/10 (10%) normal volunteers showed a hyperresponsivity to metyrapone, whereas 6/8 (7.5%) PTSD patients were hypersensitive (62). Although it is important to replicate these findings, these data are consistent with the results of the CRF challenge test in suggesting an increased stimulation of the pituitary gland that may be secondary to increased CRF stimulation in PTSD. The enhanced negative feedback provided by the increased number of glucocorticoid receptors may then serve a com-

pensatory role in regulating ACTH and corti-sol levels.

## ENHANCED NEGATIVE FEEDBACK IN PTSD: A PSYCHONEUROENDOCRINE MODEL OF SENSITIZATION

The findings observed in PTSD represent an interesting constellation of abnormalities that are consistent with several models of HPA axis functioning. The first possibility is a tonic suppression of the HPA axis. However, if the HPA axis were under a tonic suppression, it would be difficult to explain the hyperresponsivity of the pituitary to metyrapone administration, unless this effect was an artifact of the consequences of metyrapone administration on some other biological system. The results of the metyrapone study also make it unlikely that the results are due to a primary pituitary insufficiency.

The second potential model would be that of insufficient cortisol production or release from the adrenal glands (i.e., partial adrenal insufficiency). In this model, the low cortisol levels in PTSD would be due to a failure at the level of the adrenal, and increases in lymphocyte glucocorticoid receptors would reflect a compensatory change in response to low cortisol levels. Implicit in this possibility is that stress-activated neuromodulators may stimulate hypothalamic release of CRF, as well as subsequent release of ACTH from the pituitary; however, because of reduced activity of the adrenal, cortisol would be low. It would be predicted based on this model that cortisol levels would be attenuated in response to stress or provocation. To date, there is insufficient information to determine whether individuals with PTSD show an attenuated cortisol response to either traumatic or non-traumatic stressors. In fact, preliminary observations suggest that combat veterans with PTSD are capable of showing higher levels of cortisol at times when they are experiencing emotional stress (Mason, personal communication). If individuals with PTSD show the characteristic increases in cortisol following exposure to stress-

ors, this would tend to mitigate against the possibility of a partial adrenal insufficiency. Future studies are needed to address this important issue.

A third model that explains the HPA axis findings in PTSD is the model of an enhanced negative feedback inhibition (63). This model is graphed in Fig. 1. The presence of an enhanced negative feedback inhibition along one or more of the target tissues of the axis accounts for all of the current data of HPA abnormalities observed to date, and is compatible with the findings showing evidence of CRF hypersecretion as well as findings of low cortisol and augmented cortisol suppression to dexamethasone. In this model, PTSD sufferers would be expected to show chronic increases in the release of hypothalamic CRF, likely resulting from differences in neuropeptide modulation. The high levels of CRF would lead to an altered responsivity of the pituitary, as evidenced by the blunted ACTH response to CRF challenge and increased $\beta$-endorphin levels following metyrapone in PTSD. However, because of a primary alteration in glucocorticoid receptor responsivity, there would be a stronger negative feedback inhibition resulting in attenuated baseline ACTH and cortisol levels, as well as an enhanced responsivity to dexamethasone. The enhanced negative feedback model is also consistent with the recent findings of a stronger circadian rhythm of cortisol as well as the stronger signal-to-noise ratio. The stronger signal-to-noise ratio of cortisol can be seen as reflecting a system that is maximally responsive to stress, rather than a system that has adapted or habituated to stress.

The model of enhanced negative feedback is fundamentally consistent with the status of PTSD patients as being unusually responsive to stress (as opposed to being less responsive to stress, as would be indicated by models of hormone insufficiency). The PTSD patients often show exaggerated behavioral as well as biological responses to environmental challenge. The maximally low background (i.e., baseline cortisol levels) and an ability to hyperrespond to the environment as necessary (e.g., by showing exaggerated responses to neuroendocrine chal-
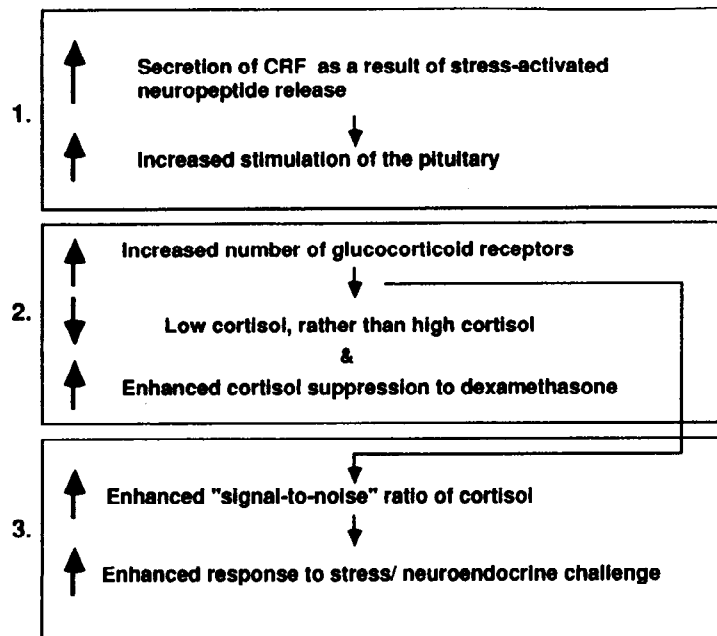
**FIG. 1.** Enhanced negative feedback of cortisol. A model of HPA axis alteration in PTSD.

lenge) may indeed reflect a type of adaptation to stress that is similar to the symptoms of hyperarousal that describe PTSD. Furthermore, the pattern of hyperresponsiveness may present not only in the HPA axis but also in the catecholamine system (64,65). (See Chapter 19 for review.)

Given the numerous modulatory influences on the HPA axis at the level of the hippocampus, hypothalamus, and pituitary, biological events that lead to the observed HPA axis alterations are likely more complex than is suggested by the model just discussed. For example, given the synergistic effects of vasopressin and CRF, it is likely that altered modulation by arginine-vasopressin may be a critical factor in the expression of HPA axis regulation (66). Furthermore, catecholamines also regulate (and are regulated by) the hormones of the HPA axis (see review (60)). Given the strong evidence for catecholamine alterations (see Chapter xx), it is likely that these neuromodulators also contribute to the alterations observed.

## EXPANDING THE STRESS RESPONSE DISORDER SPECTRUM

The HPA axis alterations in PTSD raise some interesting questions about how best to conceptualize PTSD as a stress disorder. The fact that exposure to trauma is necessary for induction of this disorder makes it reasonable to conceptualize PTSD as a "stress response." Furthermore, numerous studies have shown a relationship between the severity of trauma and the presence and severity of post-traumatic symptoms (67–70). The paradox that has arisen from the empirical data is that although PTSD is associated with stress, it does not appear to be a continuation of the typical acute response to stress (as has been suggested, perhaps erroneously, in DSM-IV). Indeed, PTSD may represent an additional type of stress response that occurs in some individuals who are exposed to trauma.

This conclusion is based on the biological data presented in this chapter, but it is also supported by recent epidemiologic studies. As re-

viewed here, the initial conception of PTSD was that it was a normal occurrence following exposure to trauma. However, at the time that the diagnosis was established, there was little information available concerning the actual prevalence of this disorder among traumatized individuals. Thus, although it was postulated that any individual could become afflicted with PTSD following exposure to extreme stress, it was unknown how many individuals did in fact develop this disorder in response to trauma exposure. It is now well established that the prevalence of PTSD is far more rare than the prevalence of trauma, with prevalence rates of PTSD ranging from 3% to 58% (67–69,71,72). The observation that only a small proportion of individuals develop prolonged symptoms following trauma supports the idea that although PTSD is a stress response, it is not inevitable.

If PTSD is not an inevitable consequence of stress, then it is not that surprising that the biological alterations observed are different from those that have been classically associated with stress responses. It might even be hypothesized that the "classical" Selye stress response profile would be more typical of individuals who have undergone trauma and do not have symptoms of PTSD. The study of the biology of PTSD, then, appears to be the study of a response observed in a subset of individuals who are exposed to trauma. For this reason, it has been suggested that most animal models of stress are likely to have very little heuristic value in promoting understanding of the pathophysiology of PTSD unless they directly model the atypical and characteristic features of the disorder (73). This point cannot be emphasized enough, because the erroneous pairing of animal models of stress with PTSD may lead to a confusion between the normative neurobiological consequences of stress and atypical neurobiological sequelae that constitute the maladaptive and rarer stress response known as PTSD.

Although the specific biological findings summarized in this chapter do not tend to support PTSD as a typical stress response, they do confirm PTSD as a distinct disorder that can be differentiated from other psychiatric conditions. Thus, the very presence of a distinctive set of

abnormalities provides biological validation of PTSD as a discrete diagnosis. In this vein it should be noted that studies of other biological systems have revealed alterations in PTSD that are also distinct from those observed in most other psychiatric conditions and differentiable from normals. In particular, psychophysiological, electrophysiological, and neurochemical investigations have provided support for an abnormal responsivity of the sympathetic nervous system and, likely, other neuromodulatory systems to traumatic (64,74–76) and nontraumatic (77,78) stimuli. These findings are reviewed in Chapter 25, and imply that there are biological changes following exposure to a trauma that are particularly associated with the symptoms of PTSD, and that can be differentiated from those observed simply as a result of stress exposure.

## IMPLICATIONS AND CONCLUSIONS

The study of PTSD, whose definition rests on being the sequelae of stress, represents an opportunity to express the effects of extreme stress on neuroendocrine functioning from a unique perspective. The findings suggest that, rather than showing a pattern of increased adrenocortical activity and resultant dysregulation of this system, individuals who suffer from PTSD show evidence of a highly sensitized HPA axis characterized by decreased basal cortisol levels, increased number of lymphocyte glucocorticoid receptors, a greater suppression of cortisol to dexamethasone, and a more sensitized pituitary gland compared to individuals without PTSD. Thus, in addition to the classic pattern of increased cortisol levels in response to stress, there may be a contrasting paradigm of cortisol abnormalities following stress, characterized by diminished cortisol levels as a result of a stronger negative feedback inhibition. This paradigm compels us to expand the stress response spectrum.

To the extent that PTSD is conceptualized as a stress disorder, the findings challenge us to regard the stress response as diverse and varied, rather than as conforming to a simple, unidirec-

tional pattern. The findings from epidemiological and longitudinal studies suggest that the search for risk factors other than exposure to trauma that may predispose or increase the likelihood of developing PTSD in individuals who sustain extreme stress may provide an important clue in defining biological heterogeneity in stress response. The neurobiology of PTSD may ultimately be related to risk factors for this disorder such as potentiality, pretrauma history, nonspecific genetic factors, and premorbid personality. These are the questions that must be addressed in the next generation of biological investigations of PTSD.

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